UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/802,358 | 03/09/2001 | Robert A. Ach | 10971722-2 | 7724 |

7590 03/25/2003

AGILENT TECHNOLOGIES, INC.
Legal Department, 51UPD
Intellectual Property Administration
P.O. Box 58043
Santa Clara, CA 95052-8043

| EXAMINER | |
|---|---|
| CHAKRABARTI, ARUN K | |
| ART UNIT | PAPER NUMBER |
| 1634 | |

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Advisory Action

| Application No. | Applicant(s) |
|---|---|
| 09/802,358 | Ach |
| **Examiner** | **Art Unit** |
| Arun Chakrabarti | 1634 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

THE REPLY FILED *Feb 3, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:
   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ they raise the issue of new matter (see NOTE below);
   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
   *See attached sheet*

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____
   Claim(s) objected to: _____
   Claim(s) rejected: _____
   Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ .

10. ☐ Other:

Claims 17-20, 24, 25, 26, 28-32, and 36-41 are rejected under 35 U.S.C. 103(a) over Martin et al. (RNA, (1998), Vol. 4, pages 226-230) in view of Cao et al. (Proceedings of the National Academy of Sciences, (USA), (1996), Vol. 93, pages 11580-11585) further in view of Stratagene Catalog (1988, page 39).

Martin et al teach the reagents and methods for end-labeling ribonucleic acids with non-radioactively labeled ribonucleotides comprising:

a non-radioactively labeled ribonucleotide which is directly detectable ; and

an eukaryotic poly(A) polymerase (Abstract and RESULTS and DISCUSSION Section, Labeling of RNA with nonradioactive nucleotides Subsection, and Figures 1-4).

Martin et al teach the reagents and methods, wherein the non-radioactively labeled ribonucleotide is a non-radioactively labeled ATP and UTP analog (Abstract).

Martin et al teach the reagents and methods, wherein the non-radioactively labeled ribonucleotide is fluorescently labeled with fluorophore fluorescein (Abstract and RESULTS and DISCUSSION Section, Labeling of RNA with nonradioactive nucleotides Subsection).

Martin et al do not teach the reagents and methods, wherein the prokaryotic poly(A) polymerase is a bacterial polymerase Escherichia coli poly(a) polymerase 1 or 2.

Cao et al. teach the reagents and methods, wherein the prokaryotic poly(A) polymerase is a bacterial polymerase Escherichia coli poly(a) polymerase 1 or 2 (Abstract and MATERIALS AND METHODS and Figures 1-5).

It would have been further *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the reagents and methods, wherein the prokaryotic poly(A) polymerase is a bacterial polymerase of Cao et al. into the composition of Martin et al, since Cao et al. state, "The identification of the gene for the second E. Coli. poly(A)

polymerase opens the way for the detailed investigation of the metabolic role of mRNA polyadenylation by studying the consequences of disruption of either or both of the poly(A) polymerase genes (Page 11585, Column 2, last sentence)". By employing scientific reasoning, an ordinary artisan would have combined and substituted a functional equivalent poly(A) polymerase of Cao et al. into the composition of Martin et al, in order to improve the detailed investigation of the metabolic role of mRNA polyadenylation. An ordinary practitioner would have been motivated to combine and substitute the reagents and methods, wherein the functional equivalent prokaryotic poly(A) polymerase is a bacterial polymerase of Cao et al. into the composition of Martin et al, in order to achieve the express advantages , as noted by Cao et al., of an invention which provides the detailed investigation of the metabolic role of mRNA polyadenylation by studying the consequences of disruption of either or both of the poly(A) polymerase genes.

Martin et al. in view of Cao et al. do not teach the motivation to combine all the reagents for end-labeling a ribonucleotide in the form of a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine a suitable container, non-radioactively labeled ribonucleotide and a prokaryotic poly(A) polymerase of Martin et al. in view of Cao et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one

quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control (page 39, column 1).

Claims 27, 34, 35, 42- 44 are rejected under 35 U.S.C. 103(a) over Martin et al. (RNA, (1998), Vol. 4, pages 226-230) in view of Cao et al. (Proceedings of the National Academy of Sciences, (USA), (1996), Vol. 93, pages 11580-11585) further in view of Stratagene Catalog (1988, page 39) further in view of Waggoner et al. (U.S. Patent 6,479,303 B1) (November 12, 2002).

Martin et al. in view of Cao et al. further in view of Stratagene Catalog teach the method of claims 17-20, 24, 25, 26, 28-32, and 36-41 as described above.

Martin et al. in view of Cao et al. further in view of Stratagene Catalog do not teach the method, wherein the polymethine fluorophore is a cyanine fluorophore chosen from Cy3, cy5, and Cy7.

Waggoner et al. teach the method, wherein the polymethine fluorophore is a cyanine fluorophore chosen from Cy3, cy5, and Cy7 (Abstract, Column 11, lines 42-60 and Table 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the reagents and methods, wherein the polymethine fluorophore is a cyanine fluorophore chosen from Cy3, cy5, and Cy7 of Waggoner et al. into the composition of Martin et al in view of Cao et al. further in view of Stratagene Catalog since Waggoner et al. states, "The development of such multichromophore complexes is particularly useful for multicolor detection systems (Column 11, lines 58-60)". An ordinary

practitioner would have been motivated to combine and substitute the reagents and methods, wherein the polymethine fluorophore is a cyanine fluorophore chosen from Cy3, cy5, and Cy7 of Waggoner et al. into the composition of Martin et al in view of Cao et al. further in view of Stratagene Catalog in order to achieve the express advantages , as noted by Waggoner et al., of an invention which provides the development of multichromophore complexes particularly useful for multicolor detection systems.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Cao et al since Cao et al states, "The identification of the gene for the second E. Coli. poly(A) polymerase opens the way for the detailed investigation of the metabolic role of mRNA polyadenylation by studying the consequences of disruption of either or both of the poly(A) polymerase genes (Page 11585, Column 2, last sentence)". Similar logic is applicable to other combination of references.

Applicant is also hereby notified in response to the arguments that the failure of Rosenmeyer et al. (U.S. Patent 5,573,913) (November 12, 1996) to end-label a ribonucleic acid with a non-radioactively labeled ribonucleic acid and a poly(A) polymerase is not persuasive. Applicant also argues that there is a structural difference between prokaryotic and eukaryotic polymerase, especially applicant refers to an upstream consensus sequence such as the AAUAAA which prokaryotic polymerase does not require for its function. This argument is not persuasive, especially in the absence of any disclosure in the specification or in the claim of the instant invention that an upstream consensus sequence such as the AAUAAA has any effect or any role to play in the end-labeling of ribonucleic acid with a non-radioactive label. Applicant is hereby notified that function of an enzyme and end-labeling of a substrate of that enzyme are two completely different phenomenon. Moreover, Martin et al (as cited above) clearly teaches to successfully end-label a ribonucleic acid with a non-radioactively labeled ribonucleic acid and a poly(A) polymerase.

Applicant then argues the 103 rejection is improper because it lacks a reasonable expectation of success.

With regard to the "lack of reasonable expectation of success" argument, The MPEP 2143.02 states

"Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the

claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Martin reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different poly(a) polymerase from Escheirchia coli were fluorescently labeled and were actually experimentally studied and found to be functional (Example 7). This evidence of functionality trumps the attorney arguments, which argues that Martin reference is an invitation to research, since Mertin steps beyond research and shows the functional product.

Accordingly, all previous 103(a) rejection along with a new 103(a) rejection is hereby properly maintained.

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600